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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/171,625	07/02/1999	HUBERT KOSTER	24743-2302US	8272

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EXAMINER

PONNALURI, PADMASHRI

ART UNIT	PAPER NUMBER
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1639

DATE MAILED: 07/15/2003

34

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/171,625

Applicant(s)

Koster et al

Examiner

Padmashri Ponnaluri

Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on Apr 23, 2003
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 4 and 11-16 is/are pending in the application.
- 4a) Of the above, claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 4 and 11-16 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. _____.
 - ☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

- 14) ☒ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892) 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948) 5) ☐ Notice of Informal Patent Application (PTO-152)
- 3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____ 6) ☐ Other:

Art Unit: 1639

DETAILED ACTION

1. The request filed on 4/23/03 for a Continued Prosecution Application (CPA) under 37 CAR 1.53(d) based on parent Application No. 09/171,625 is acceptable and a CPA has been established. An action on the CPA follows.
2. The response filed on 4/23/03 has been fully considered and entered into the application.
3. Claims 4 and 11-16 are currently pending and are being examined in this application.
4. Applicant's election without traverse of group I, claims 4, 11-16; and election of trityl ether as linkage, and phosphate group as reactive moiety, in Paper No. 21, filed on 2/22/02, is acknowledged.
5. This application has been filed with informal drawings which are acceptable for examination purposes only. Formal drawings will be required when the application is allowed.
6. The lengthy specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.
7. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.
8. Claims 4 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

Art Unit: 1639

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

The instant claims briefly recite a process for generating a combinatorial library, by preparing a plurality of immobilized molecules (nucleoside or nucleotide), where in each molecule (each nucleotide or nucleoside) contains 3 to 10 reactive moieties, each reactive moiety is blocked by a blocking group, and at least three blocking groups on a molecule are independently removable under at least three different conditions; and removing the blocking group and derivitizing the resulting moiety in a preprogrammed, regioselective manner to generate a combinatorial library.

The 'each molecule (nucleotide or nucleoside) contains 3 to 10 reactive moieties' claimed in Claims 4, 11-16 has no clear support in the specification and the claims as originally filed. The specification discloses the use of 3 or more reactive groups on more than one nucleotide and which are protected by 3 or more different protecting groups. The subject matter claimed in claims 4, 11-16 broadens the scope of the invention as originally disclosed in the specification.

If applicants disagree, applicant should present a detailed analysis as to why the claimed subject matter has clear support in the specification.

9. Claims 4 and 11-16 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey

Art Unit: 1639

to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

The instant claims briefly recite a process for generating a combinatorial library, by preparing a plurality of immobilized molecules (nucleoside or nucleotide), where in each molecule contains 3 to 10 reactive moieties, each reactive moiety is blocked by a blocking group, and at least three blocking groups on a molecule are independently removable under at least three different conditions; and removing the blocking group and derivitizing the resulting moiety in a preprogrammed, regioselective manner to generate a combinatorial library.

The present claims are directed to generating a combinatorial library in which there is no claimed structure or other identifying characteristics presented with respect to the final combinatorial compounds and types of blocking groups used such that they are removable under at least three different conditions.

The specification description is directed to synthesis of oligonucleotide synthesis using modified nucleobases (more than one nucleobase) with multiple protecting groups attached (note that a single nucleobase does not have 3 or more protecting groups attached) which clearly do not provide an adequate representation regarding the open ended claimed method of combinatorial compound library method of the presently claimed invention. The specification teaches the use of specific protecting groups (npe, npeoc, npc) and reaction conditions at which the protecting groups are removed orthogonally. The instant claimed method recites the use

Art Unit: 1639

immobilized nucleoside or nucleotide as core molecule which have 3 or more protecting groups which are deprotected using 3 different conditions.

With regard to the description requirement, Applicants' attention is directed to The Court of Appeals for the Federal Circuit which held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1405 (1997), quoting *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original)[The claims at issue in *University of California v. Eli Lilly* defined the invention by function of the claimed DNA (encoding insulin)].

Although directed to DNA compounds, this holding would be deemed to be applicable to any compound or method; which requires a representative sample of compounds and/or a showing of sufficient identifying characteristics to demonstrate possession of the claimed generic(s).

In the present instance, the claimed invention contains no identifying characteristics regarding the combinatorial library of compounds prepared using the claimed method. The core structure contains more than one modified nucleobases, thus the molecules synthesized using the claimed method may result in different compounds. The claimed invention is drawn to the use of nucleotide which has 3 or more protecting groups protected by 3 or more different protecting groups removable by at least 3 different reaction conditions. However, the specification disclosure

Art Unit: 1639

is based on the use of 3 different protecting groups present on an oligomer and methods for deprotecting the 3 different protecting groups at different reaction conditions. The specification does not disclose the use of an immobilized single nucleotide with 3 reactive moieties which are removed by 3 different reaction conditions.

Additionally, the narrow scope of examples directed to the use of specific protection groups and reaction conditions present on an oligomer which are clearly not representative of the scope of the presently claimed method.

10. Claims 4, 11-16 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the use of specific linkers (npeoc, npc and npe) with specific reactions (deprotection reactions), does not reasonably provide enablement for any type of protecting groups and deprotection reagents. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The instant claims briefly recite a process for generating a combinatorial library, by preparing a plurality of immobilized molecules (nucleoside or nucleotide), where in each molecule contains 3 to 10 reactive moieties, each reactive moiety is blocked by a blocking group, and at least three blocking groups on a molecule are independently removable under at least three different conditions; and removing the blocking group and derivitizing the resulting moiety in a preprogrammed, regioselective manner to generate a combinatorial library.

Art Unit: 1639

The specification disclosure is based on the use of specific protecting groups and specific reactions and conditions to remove the protecting groups, such that the blocking groups (protecting groups) are activated in regioselective manner. The specification pages 7- 10 disclose the selective orthogonal deprotection . The specification discloses specific protecting groups (reactive in acidic or neutral or basic conditions). The specification discloses that 'selective and orthogonal deprotection are possible if at the linkagesof oligomers, deprotections are selectively done...'. The specification disclosure is based on the use of specific protecting groups at selective positions on the molecules, such that they are regioselectively removed using deprotection reagents.

The factors to be considered in a determination of undue experimentation are disclosed in *In re Wands* (U. S. P. Q. 2d 1400: CAFC 1988) which include: the quantity of experimentation necessary; . the amount of direction or guidance presented; the presence or absence of working examples; . the nature of the invention; the state of the prior art; the predictability of the art; and the breadth of the claims.

A number of factors would prevent one of ordinary skill in the art from practicing (making and using) the invention without undue experimentation, which are summarized as follows:

a. The specification fails to give adequate direction and guidance as to the means of making combinatorial libraries using any type of protecting groups to protect any reactive functional groups using deprotection reagents. The specification discloses that the deprotection conditions of one specific protecting group is selected such a way so that the deprotection would not not

Art Unit: 1639

effect the other protecting groups. The specification discloses that deprotection of npeoc/npe would not effect the trityl ether bond of npe bond. The specification discloses that the deprotection conditions has to be determined so that the conditions would not effect other protecting groups. For example, the specification discloses that 'the stability of R4 during deprotection at 1, 3 and 4 is not necessary, and if R4 is being removed during deprotection at position 4 using reagent IV,... the substitution at position 2 has to be carried out before, and R4 must be stable with reagent II, to guarantee a sequence specific derivitization at position 2. Thus, the use of protecting groups and deprotection reagents are specific, and the sequence of deprotection reactions are specific or predetermined based on the stability of the protecting groups. The specification disclosure is based on the use of 3 or more protection groups which are present on **an oligonucleotide not on a single molecule (nucleotide or nucleobase as in the claims)**.

b. The working examples are directed to the use of specific protecting groups and deprotection reagents or conditions and the use 3 or more protecting groups on oligomer not on a single nucleobase.

c. The breadth of the claims are open-ended regarding the use of protecting groups and deprotection reaction conditions, and the order of the deprotection reactions and the also the term molecule.

d. The art is inherently unpredictable because the use of protecting groups in a specific position may be unstable during the deprotection conditions, and result in unwanted reactions to occur.

Art Unit: 1639

In view of the quantity of experimentation necessary, the limited working examples, the unpredictability of the art, the lack of sufficient guidance in the specification, it would take undue trials and errors to practice the claimed invention.

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 4, 11-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 4, 11-16 recite 'plurality of immobilized molecules selected from a nucleoside or nucleotide, wherein each molecule contains 3 to 10 reactive moieties...', it is not clear whether applicants mean that each nucleotide has 3 to 10 reactive moieties' or plurality of molecules (i.e., more than one nucleoside or nucleotide together) have 3 or more protecting groups. The specification examples in the schemes are all drawn to the use of different protecting groups on different nucleobases. Thus, applicants are requested to clarify.

13. No claims are allowed.

14. Applicant's arguments filed on 4/23/03 have been fully considered but they are not persuasive.

Art Unit: 1639

Applicants arguments regarding the scope enablement rejection of the claims has been fully considered and are not persuasive. Applicants arguments refer to several documents which refer the use of different protecting groups. However, the references do not specifically teach the use of more than 3 protecting groups which can be cleaved at three different reaction conditions, and all the three or more protecting groups are present on one nucleotide or nucleobase.

Further applicants refer to scheme 3 which uses DMTr and Fmoc as protecting groups. However, in the disclosed scheme 3 these protecting groups are not used to protect 3 or reactive moieties of a single nucleobase which is immobilized to a solid support.

Applicants arguments based on scheme 1 is not persuasive, since scheme 1 discusses the stability of a single protecting group nps, which is different from the claimed method use of 3 or more protecting groups. Applicants further refer to table 1 in the specification. However, the example or table 1 refers to the oligomer 3 of scheme 1 (Note in the instant claims the molecule refers to a nucleotide or nucleoside not an oligomer as in the arguments), in which 3 different protecting groups which are deprotected or cleaved at different reaction conditions. Thus, applicants response is to persuasive. The specification disclosure does not sufficiently teach the use of 3 or more protecting groups on a single nucleobase which are cleavable at three different reaction conditions.

Art Unit: 1639

Any inquiry concerning this communication or earlier communications from the examiner should be directed to P. Ponnaluri whose telephone number is (703) 305-3884. The examiner is on *Increased Flex Schedule* and can normally be reached on Monday to Friday from 7.00 AM to 3.30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached on (703) 306-3217. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

P. Ponnaluri
Primary Patent Examiner
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Art Unit 1639
17 July 2003


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